Ofd1, a human disease gene, regulates the length and distal structure of centrioles.

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Public Summary:
We used embryonic stem cells to examine the function of a human disease gene, OFD1. Disease mutations in OFD1 affected the ability to form a primary cilium, a structure involved in sensing a wide variety of environmental stimuli and affected in some forms of blindness and kidney disease. Also, we determined that OFD1 caps centrioles, important regulators of the cell cytoskeleton, to regulate their length.

Scientific Abstract:
Centrosomes and their component centrioles represent the principal microtubule organizing centers of animal cells. Here, we show that the gene underlying orofaciodigital syndrome 1, Ofd1, is a component of the distal centriole that controls centriole length. In the absence of Ofd1, distal regions of centrioles, but not procentrioles, elongate abnormally. These long centrioles are structurally similar to normal centrioles but contain destabilized microtubules with abnormal posttranslational modifications. Ofd1 is also important for centriole distal appendage formation and centriolar recruitment of the intraflagellar transport protein Ift88. To model OFD1 syndrome in embryonic stem cells, we replaced the Ofd1 gene with missense alleles from human OFD1 patients. Distinct disease-associated mutations cause different degrees of excessive or decreased centriole elongation, all of which are associated with diminished ciliogenesis. Our results indicate that Ofd1 acts at the distal centriole to build distal appendages, recruit Ift88, and stabilize centriolar microtubules at a defined length.